## ATENT COOPERATION TRATY

### From the INTERNATIONAL BUREAU

### **PCT**

#### **NOTIFICATION OF ELECTION**

(PCT Rule 61.2)

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To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202

Date of mailing (day/month/year)
07 November 2000 (07.11.00)

in its capacity as elected Office

International application No.
PCT/CA00/00289

International filing date (day/month/year)
16 March 2000 (16.03.00)

Applicant's or agent's file reference 1038-1025

**ETATS-UNIS D'AMERIQUE** 

Priority date (day/month/year)
16 March 1999 (16.03.99)

**Applicant** 

LOOSMORE, Sheena, M. et al

1.	The designated Office is hereby notified of its election made:
	X in the demand filed with the International Preliminary Examining Authority on:
	11 October 2000 (11.10.00)
	in a notice effecting later election filed with the International Bureau on:
2.	The election X was
	was not
	made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland

Authorized officer

**Nestor Santesso** 

Telephone No.: (41-22) 338.83.38

Facsimile No.: (41-22) 740.14.35

# PATENT COOPERATION TREATY

### **PCT**

# NOTIFICATION THAT INTERNATIONAL APPLICATION CONSIDERED TO BE WITHDRAWN

(PCT Article 14(1), (3) or (4) and Rule 29.1)

### From the INTERNATIONAL BUREAU

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as designated Office

Date of mailing (day/month/year) 28 August 2001 (28.08.01)	IMPORTANT NOTIFICATION
International application No. PCT/CA00/00289	International filing date (day/month/year) 16 March 2000 (16.03.00)
Applicant	
CONNAUGHT LABORATORIES LIMITED et al	

1.	The International Bureau hereby gives notice that the receiving Office has, on the date indicated below, notified to the
	applicant that the international application is to be considered withdrawn:

01 June 2001 (01.06.01)

A copy of this notification has been sent to the International Preliminary Examining Authority.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Authorized officer

V. Gross (Fax 338.87.40)

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION PEATY REC'D 19 JUL 2001
WIPO



## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference		Con Netification of Transmitted of Lawrence
1038-1025	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No.	International filing date (day/mont	h/year) Priority date (day/month/year)
PCT/CA00/00289	16/03/2000	16/03/1999
International Patent Classification (IPC) or na C07K14/00	ational classification and IPC	
Applicant		
CONNAUGHT LABORATORIES LI	MITED et al	
This international preliminary exam and is transmitted to the applicant a	ination report has been prepare according to Article 36.	d by this International Preliminary Examining Authority
2. This REPORT consists of a total of	9 sheets, including this cover s	heet.
been amended and are the bas	d by ANNEXES, i.e. sheets of the sis for this report and/or sheets of the Administrative Instruction	ne description, claims and/or drawings which have containing rectifications made before this Authority ons under the PCT).
These annexes consist of a total of	8 sheets.	
3. This report contains indications rela	ting to the following items:	
Ⅰ       Basis of the report		
Ⅱ □ Priority		
III   Non-establishment of o	pinion with regard to novelty, inv	entive step and industrial applicability
IV   Lack of unity of invention	n	•
V 🛛 Reasoned statement ur citations and explanatio	nder Article 35(2) with regard to i	novelty, inventive step or industrial applicability;
VI   Certain documents cite		
VII D Certain defects in the in	ternational application	
VIII   Certain observations on	the international application	
Date of submission of the demand	Date of c	completion of this report
11/10/2000	17.07.20	01
Name and mailing address of the international	Authorize	ed officer
preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656	Zellner,	E
Fax: +49 89 2399 - 4465	Telephon	ie No. +49 89 2399 8427

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA00/00289

				-	
I.	Basis of the report			t taka which	have been furnished to
1.		ments of the international response to an invitation of this report since they do			
	1-13,16,17, 19-63	as originally filed			
	14,15,18	as received on	22/06/2001	with letter of	22/06/2001
	Claims, No.:				
	1-29	as received on	22/06/2001	with letter of	22/06/2001
	Drawings, sheets:				
	1/83-83/83	as originally filed			·
	Sequence listing pa	rt of the description, pag	jes:		
	2-75, filed with the let				
2		nguage, all the elements r e international application	narked above were a was filed, unless oth	available or furnishe erwise indicated un	ed to this Authority in the der this item.
	-	e available or furnished to			
	☐ the language of             ☐ the language of	a translation furnished for	the purposes of the	international search	(under Rule 23.1(b)).
	□ the lenguage of	publication of the internati	onal application (und	der Rule 48.3(b)).	•
	the language of 55.2 and/or 55.3	a translation furnished for 3).	the purposes of inte	rnational preliminar	y examination (under Rule
;	<ol> <li>With regard to any n international prelimir</li> </ol>	nucleotide and/or amino a nary examination was carr	acid sequence disclined out on the basis	osed in the internati of the sequence list	onal application, the ing:
	☐ contained in the	e international application i	n written form.		
	☐ filed together w	ith the international applica	ation in computer rea	adable form.	
		equently to this Authority in			
	₩ furnished subse	equently to this Authority in	computer readable	form.	_
		that the subsequently furn	ished written sequer een furnished.	nce listing does not g	go beyond the disclosure i
	☐ The statement	that the information record	led in computer read	lable form is identica	al to the written sequence

listing has been furnished.

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA00/00289

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4	. Th	e ar	nendments have r	esulted in the cancellation of:
		th	e description,	pages:
			e claims,	Nos.:
			ie drawings,	sheets:
į	5. 🗵	T	his report has bee onsidered to go be	n established as if (some of) the amendments had not been made, since they have been eyond the disclosure as filed (Rule 70.2(c)):
		(i	Any replacement s eport.) see separate shee	heet containing such amendments must be referred to under herry and same
	6. <b>A</b>	ddit	ional observations	, if necessary:
	<b>IV. L</b> 1. li	.ack	c of unity of inven	tion ation to restrict or pay additional fees the applicant has:
	[	J	restricted the clain	ns.
	ļ	Ø	paid additional fee	s.
	ļ		paid additional fee	
			neither restricted	nor paid additional fees.
	2.		co 4 not to invite	nd that the requirement of unity of invention is not complied and chose, according to Rule the applicant to restrict or pay additional fees.
`	3.	This	s Authority conside	ers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is
)			complied with.	
		☒	- coo congrate sh	n for the following reasons:  neet  neet
	4.	Co	nsequently, the fol amination in estab	llowing parts of the international application were the subject of international preliminary lishing this report:
		X	all parts.	
				g to claims Nos
	V	. Re	easoned stateme tations and expla	nt under Article 35(2) with regard to novelty, inventive step or industrial applicability; nations supporting such statement
	1		tatement	

## INTERNATIONAL PRELIMINARY **EXAMINATION REPORT**

International application No. PCT/CA00/00289

Novelty (N)

Yes:

Claims 1-2,4-29

No:

Claims 3

Inventive step (IS)

Claims 4 Yes:

No:

Claims 1-3,5-29

Industrial applicability (IA)

Claims 1-29 Yes:

Claims No:

2. Citations and explanations see separate sheet

# VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made: see separate sheet

# INTERNATIONAL PRELIMINARY Inte

D1: WO 96 30519 A (UNIV WASHINGTON ;UNIV ST LOUIS (US); ST GEME JOSEPH W III (US); BA) 3 October 1996 (1996-10-03)

D2: GEME J W S ET AL: 'CHARACTERIZATION OF THE GENETIC LOCUS ENCODING HAEMOPHILUS INFLUENZAE TYPE B SURFACE FIBRILS' JOURNAL OF BACTERIOLOGY, US, WASHINGTON, DC, vol. 178, no. 21, November 1996 (1996-11), pages 6281-6287, XP000863110 ISSN: 0021-9193

D3: BARENKAMP S J ET AL: 'IDENTIFICATION OF A SECOND FAMILY OF HIGH-MOLECULAR-WEIGHT ADHESION PROTEINS EXPRESSED BY NON-TYPABLE HAEMOPHILUS INFLUENZAE' MOLECULAR MICROBIOLOGY,GB,BLACKWELL SCIENTIFIC, OXFORD, vol. 19, no. 6, 1996, pages 1215-1223, XP000579265 ISSN: 0950-382X

#### Item I

The amendment of Claim 3 is not allowable under Articles 19(2) and 34 (2) (b) PCT. Additional feature "N-truncated protein having the ability to bind to human epithelial cells" is not disclosed in the description as originally filed. For the N-truncated hia proteins it is only described that immunization causes protection against colonization (see Examples).

### Item IV

The present set of claims are not linked in manner so as to form a single general inventive concept as required under Rule 13(1) PCT.

The problem underlying the invention of the present application is the provision of a set of nucleotide and amino acid sequences of adhesion (Hia) from non-typeable strains of Haemophilus influenzae.

The solution is represented by the set of amino- and nucleic acid sequences as set forth in SEQ. ID. Nos 23-36.

The international patent application WO9630519 discloses adhesins from non-typeable strains of Haemophilus influenzae, as well as methods for their recombinant production

## INTERNATIONAL PRELIMINARY **EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/CA00/00289

and their use in immunogenic compositions and production of antibodies (see abstract, example 3, page 82-84).

Genes from non-typeable H. influenzae coding for Hia adhesins are also disclosed by St. Geme et al. in Infection and Immunity (1998, p. 364-368, see abstract).

Therefore the concept of DNA encoding adhesins from non typeable H. influenzae is not new. In consequence, the different adhesins of the present application fall a posteriori into 6 groups of alleged inventions.

- 1. Claims 1-27 (partially)
  - An isolated and purified nucleic acid molecule having a sequence as set forth in SEQ ID NO. 23 encoding an polypeptide of a Haemophilus influenzae adhesion having the primary structure as set forth in SEQ ID NO. 24. Vectors for the recombinant production of said adhesion, immunogenic compositions containing the same.
- An isolated and purified nucleic acid molecule having a sequence as set forth in 2. SEQ ID NO. 27 encoding an polypeptide of a Haemophilus influenzae adhesion having the primary structure as set forth in SEQ ID NO. 28. Vectors for the recombinant production of said adhesion, immunogenic compositions containing the same.
- An isolated and purified nucleic acid molecule having a sequence as set forth in 3. SEQ ID NO. 29 encoding an polypeptide of a Haemophilus influenzae adhesion having the primary structure as set forth in SEQ ID NO. 30. Vectors for the recombinant production of said adhesion, immunogenic compositions containing the same.
- An isolated and purified nucleic acid molecule having a sequence as set forth in 4. SEQ ID NO. 31 encoding an polypeptide of a Haemophilus influenzae adhesion having the primary structure as set forth in SEQ ID NO. 32. Vectors for the recombinant production of said adhesion, immunogenic compositions containing the same.

# INTERNATIONAL PRELIMINARY Inte

- 5. An isolated and purified nucleic acid molecule having a sequence as set forth in SEQ ID NO. 33 encoding an polypeptide of a Haemophilus influenzae adhesion having the primary structure as set forth in SEQ ID NO. 34. Vectors for the recombinant production of said adhesion, immunogenic compositions containing the same.
- 6. An isolated and purified nucleic acid molecule having a sequence as set forth in SEQ ID NO. 35 encoding an polypeptide of a Haemophilus influenzae adhesion having the primary structure as set forth in SEQ ID NO. 36. Vectors for the recombinant production of said adhesion, immunogenic compositions containing the same.

#### Item V

#### 1. Novelty:

Claim 3 is not allowable under Article 33 (2) PCT.

Due to the generic and broad definition (especially the wording "truncated" and "expressible" of said claim (see also item VIII) all sorts of H. influenza adhesion encoding nucleotides fall under the definition of Claim 3.

In other words all adhesion nucleotides encoding for any adhesion being shorter (i.e. truncations of only one or two amino acids) than an adhesion of the present application lies within the definition such as those of D1 (see e.g. sequence comparisons of the Search Examiner page 6, in comparison with GSP:R99394 is shorter than no SEQ ID 28).

## 2. Inventive step

D1 is considered to represent the closest prior art document. D1 teaches Haemophilus adhesion proteins nucleic acids and derived vaccines. SEQ ID NO 36 of the present application has 97% identity with the amino acid sequence of D1, SEQ ID NO 32 has 79% identity with the amino acid sequence of D1 (Sequence Comparisons of the Search Examiner). The problem of the present application is to provide further H. influenza adhesions

# INTERNATIONAL PRELIMINARY Inte

International application No. PCT/CA00/00289

proteins and their encoding genes. As soon as one family member of the Haemophilus influenza adhesion protein, its gene the recombinant production and its immunological use is known, it is routine for a skilled person to determine further similar members from other strains of said proteins their immunogenic fragments and their encoding genes.

In this case the cloning and expression, although requiring much work, does not pose such problems so that there was no reasonable expectation of success. For a skilled person it is also obvious to provide non-specified truncated versions of said genes or proteins having no particular unexpected effect (Claim 3).

In consequence, the present claims 1-3, 5-29 are not allowable under Article 33 (3) PCT.

The specific truncated Hia proteins of Claim 4 fulfil the requirements under Article 33(2) and (3) PCT.

The essential difference with D1 is the truncated form wherein the signal sequence is deleted causing a higher expression in E. coli. Said truncated proteins are still immunogenic (see Examples).

The problem of the present application can thus be defined as the provision of alternative hia proteins which can be produced recombinantly in a high amount still causing immunity.

The solution i.e. the truncated hia proteins of claim 4 are not derivable from D1 or any other document cited in the Search Report.

#### Item VIII

 Claim 2 is formulated in terms of a "product by process". In the PCT contracting states no unified criteria exist concerning this type of claims. Before the EPO such claims, defined in terms of a product by process of manufacture are only admissible if the product as such fulfils the requirements of patentability, i.e. if the products are novel and inventive and if the product cannot be defined by true technical features (Article 6 PCT).

The same applies to claim 15.

# International application No. PCT/CA00/00289

## INTERNATIONAL PRELIMINARY **EXAMINATION REPORT - SEPARATE SHEET**

- Independent Claim 3 does not disclose any true technical features. The only 2. characteristic of the claimed nucleic acids is that they are "truncated" and "expressible as inclusion bodies". In consequence, said claim is vague and thus not clear (Article 6 PCT).
- The Applicant should prove whether the strains of Claim 27 are known by the 3. skilled person. Otherwise said claim is not clear.

generate the sites. Upperstrand (SEQ ID No.: 50) lower strand (SEQ ID No.: 51).

Figure 7A shows the construction of plasmids DS-2242-1 and DS-2242-2 that contain the T7 promoter and full-length NTHi strain 33 hia gene, the E. coli cer gene and the kanamycin resistance gene. Restriction enzyme sites are: A, AlwN I; B, BamH I; Bg, Bgl II; H, Hind III; K, Kpn I; N, Nde I; Ps, Pst I; R, EcoR I; S, Sal I; Sm, Sma I; Xb, Xba I; Xho, Xho I. Other abbreviations are: T7p, T7 promoter; ApR, ampicillin resistance; kanamycin KanR, resistance; tt2, trpA; transcription terminator from 1 transcription terminator 2 from T7 gene 10.

Figure 7B shows the oligonucleotides used to generate the 5'-end of the strain 33 his gene coding strand (SEQ ID No.: 52), complementary strand (SEQ ID No.: 53), and encoded amino acid sequence (SEQ ID No.: 54).

Figure 8A shows the construction of plasmid DS-2340-2-3 that contains the T7 promoter and the V38 his gene from strain 33, the E. coli cer gene and the kanamycin resistance gene. Restriction enzyme sites are: B, BamH I; Bg, Bgl II; H, Hind III; N, Nde I; Ps; PSC I; R, ECOR I; S, Sal I; Sn, SnaB I; Xb, Xba I. T7 promoter; abbreviations are: T7p, Other ampicillin resistance; KanR, kanamycin resistance; ttl, transcription terminator 1 from tt2, transcription terminator 2 from T7 gene 10.

Figure 8B shows the oligonucleotides used to PCR amplify the 5'-end of the truncated hia gene. Sense (6286.SL): SEQ ID No: 60, encoded amino acids SEQ ID

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No: 61; antisense (6287.SL) SEQ ID No: 18, complement SEQ ID No: 19, encoded amino acids SEQ ID No: 20.

Figures 9A and 9B show the construction of plasmids DS-2447-2 and DS-2448-17, that contain tandem copies of the T7 V38 hia (11) and T7 V38 hia (33) genes, respectively. Restriction enzyme sites are: B, BamH I; Bg, Bgl II; H, Hind III; Ps; Pst I; R, EcoR I; S, Sal I; Xb, Xba I. Other abbreviations are: T7p, T7 promoter; ApR, ampicillin resistance; KanR, kanamycin resistance; CAP, calf alkaline phosphatase; ttl, transcription terminator 1 from trpA; tt2, transcription terminator 2 from T7 gene 10.

Figure 10 shows the expression of rHia. Panel A: lane 1, full-length rHia (11) no induction; lane 2, full-length rHia (11); lane 3, E21 rHia (11); lane 4, T33 rHia (11); lane 5, V38 rHia (11); lane 6, N52 rHia (11). Panel B: lane 1, V38 rHia (11) no induction; lane 2, V38 rHia (11); lane 3, V38 rHia (11)/cer.

Figure 11 shows a purification scheme for rHia proteins. Abbreviations are: SP, supernatant; PPT, precipitate; DTT, dithiothreitol; OG, octyl glucoside; (x) means discarded.

Figure 12, having panels A and B, shows the SDS-PAGE analysis of purified rHia. Panel A shows purified V38 rHia protein from strain 11 and panel B shows purified V38 rHia protein from strain 33. Lane 1, molecular weight markers; lane 2, whole-cell lysate; lane 3, crude extract; lane 4, purified rHia protein.

Figure 13, having panels A, B and C, shows the stability of V38 rHia (11). Panel A shows samples stored at 4°C without glycerol. Panel B shows samples

AMENDED SHEET
Empfansszeit ZZ-JUHI 14-44

Moraxella catarrhalis high molecular weight proteins (200 kDa) from strains 4223 and LES-1 (SEQ ID Nos.: 48, Asterisks within sequences indicate stop codons, indicated sequence they below the but Dots indicate identical residues. The homology. direct . prepared by alignments were sedneuce sequences the the amino acid comparison of respective proteins.

Figure 29 shows the oligonucleotides used to PCR amplify the 5' end of the his gene at the S44 truncated position. Sense (6817.SL) SEQ ID No: 55, encoding amino acids SEQ ID No: 56; antisense (6818.SL) SEQ ID No: 57, complement SEQ ID No: 58, encoded amino acids SEQ ID No: 59.

Figure 30 shows the construction of plasmid JB-2930-3 that contains the S44 his gene from NTHi strain 11 and the E. coli cer gene and the T7 promoter. Restriction enzyme sites are: B, BamH I; Bg, Bgl II; K, Kpn I; N, Nde I; P, Pst I; R, EcoR I; S, Sal I; Sm, Sma Other Xho, Xho I. Xba I; Xb, Sty I; abbreviations are: T7p, T7 promoter; ApR, ampicillin kanamycin resistance; CAP, resistance; KanR, alkaline phosphatase; ttl transcription terminator 1 from trpA; tt2, transcription terminator 2 from T7 gene 10.

Figure 31 shows SDS-PAGE analysis of the expression of rhia from S44. Lane 1, expression from pET S44 vector at time 0 (no induction); lane 2 expression from pET S44 vector after 4 hours induction; lane 3 expression from JB-2930-3 after 4 hours induction.

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### <u>CLAIMS</u>

- 1. An isolated and purified nucleic acid molecule encoding a Haemophilus influenzae adhesin (Hia) protein of a strain of Haemophilus influenzae having:
  - (a) a DNA sequence selected from the group consisting of those shown in Figures 18, 20, 21, 22, 23, 24 and 25 (SEQ ID Nos: 23, 27, 29, 31, 33, 35, 37); or
  - (b) a DNA sequence encoding a Haemophilus influenzae adhesin (Hia) protein having an amino acid sequence selected from the group consisting of those shown in Figures 18, 20, 21, 22, 23, 24 and 25 (SEQ ID Nos: 24, 28, 30, 32, 34, 36, 38).
- 2. An isolated and purified nucleic acid molecule encoding an N-truncated Haemophilus influenzae adhesin (Hia) protein of a strain of Haemophilus Influenzae which is amplifiable by a pair of nucleotides which are selected from the group consisting of:

SEQ ID No: 7 and SEQ ID No: 15 SEQ ID No: 9 and SEQ ID No: 15 SEQ ID No: 11 and SEQ ID No: 15 SEQ ID No: 13 and SEQ ID No: 15 SEQ ID No: 55 and SEQ ID No: 57

- 3. An isolated and purified nucleic acid encoding an N-truncated Haemophilus influenzae adhesin (Hia) protein of a strain of Haemophilus influenzae expressed as inclusion bodies, said N-truncated protein having the ability to bind to human epithelial cells.
- The nucleic acid molecule of claim 3 which encodes a truncated His protein selected from the group consisting of the E21, T33, V38 and N52 truncations of Haemophilus influenzae strain 11 and the V38 truncation of Haemophilus Influenzae strain 33.
- 5. A vector for transforming a host comprising the nucleic acid molecule of claim 1.
- 6. A vector for transforming a host comprising the nucleic acid molecule of any one of claims 2 to 4.
- 7. The vector of claim 5 or 6 which is a plasmid vector.
- 8. The vector of claim 7 wherein said plasmid vector has the identifying characteristics of a plasmid which is selected from the group consisting of:

**SIMBAS**→

DS-2008-2-3 as shown in Figure 1A
DS-2186-1-1 as shown in Figure 5A
DS-2201-1 as shown in Figure 5A
DS-2186-2-1 as shown in Figure 5A
DS-2168-2-6 as shown in Figure 5A
IA-191-3-1 as shown in Figure 32

- 9. A vector for transforming a host, comprising a nucleic acid molecule encoding a full-length *Haemophilus Influenzae* adhesin (Hia) protein as claimed in claim 1 or N-truncated *Haemophilus Influenzae* adhesin (Hia) protein as claimed in any one of claims 2 to 4 and a promoter operatively connected to said nucleic acid molecule for expression of said full-length or truncated Hia protein.
- 10. The vector of claim 9 further comprising the cer gene of E. coli.
- 11. The vector of claim 9 which is a plasmid vector.
- 12. The vector of claim 11 wherein said plasmid vector has the identifying characteristics of a plasmid vector which is selected from the group consisting of:

BK-96-2-11 as shown in Figure 6A
DS-2242-1 as shown in Figure 7A
DS-2242-2 as shown in Figure 7A
DS-2340-2-3 as shown in Figure 8A
DS-2447-2 as shown in Figure 9A
DS-2448-17 as shown in Figure 9B
JB-2930-3 as shown in Figure 32

- 13. A host cell transformed by a vector as claimed in claim 5, 6 or 9 and expressing a protective *Haemophilus influenzae* adhesin (Hia) protein of a non-typeable strain of *Haemophilus*.
- 14. The host cell of claim 13 which is a strain of E. coll.
- 15. A recombinant protective Haemophilus influenzae adhesin (Hia) protein of a strain of Haemophilus influenzae producible by the transformed E. coli of claim 14 or an immunogenic fragment thereof.

- 16. An Immunogenic composition, comprising at least one immunologically-active component selected from the group consisting of:
- (A) an isolated and purified nucleic acid molecule encoding a Haemophilus influenzae adhesin (Hia) protein of a strain of Haemophilus influenzae having:
  - (a) a DNA sequence selected from the group consisting of those shown in Figures 18, 20, 21, 22, 23, 24 and 25 (SEQ ID Nos: 23, 27, 29, 31, 33, 35, 37); or

SIMBAS→

- (b) a DNA sequence encoding a Haemophilus influenzae adhesin (Hia) protein having an amino acid sequence selected from the group consisting of those shown in Figures 18, 20, 21, 22, 23, 24 and 25 (SEQ ID Nos: 24, 28, 30, 32, 34, 36, 38);
- (B) an isolated and purified nucleic acid molecule encoding an N-truncated Haemophilus influenzae adhesin (Hia) protein of a strain of Haemophilus influenzae which is amplifiable by a pair of nucleotides which are selected from the group consisting of:

SEQ ID No: 7 and SEQ ID No: 15 SEQ ID No: 9 and SEQ ID No: 15 SEQ ID No: 11 and SEQ ID No: 15

SEQ ID No: 13 and SEQ ID No: 15

SEQ ID No: 55 and SEQ ID No: 57;

- (C) an isolated and purified nucleic acid molecule encoding a truncated Haemophilus influenzae adhesin (Hia) protein of a strain of Haemophilus influenzae expressed as inclusion bodies, said N-truncated protein having the ability to bind to human epithelial cells; and
- (D) a recombinant protective Haemophilus influenzae adhesin (Hia) protein of a strain of Haemophilus influenzae producible by a strain of E. coli transformed by an expression vector as claimed in claim 5, 6 or 9; and

a pharmaceutically-acceptable carrier therefor.

17. The Immunogenic composition of claim 16 formulated as a vaccine for in vivo administration to protect against disease caused by Haemophilus.

- 4 -

- 18. The immunogenic composition of claim 16 in combination with a targeting molecule for delivery to specific cells of the immune system or to mucosal surfaces.
- 19. The immunogenic composition of claim 16 formulated as a microparticle, capsule or liposome preparation.
- 20. The immunogenic composition of claim 16 further comprising an adjuvant.
- 21. A method for inducing protection against disease caused by Haemophilus, comprising administering to a susceptible host an effective amount of the immunogenic composition of claim 16.
- 22. The method of claim 21 wherein the susceptible host is a human.
- 23. A method for the production of a protective Haemophilus influenzae adhesin (Hia) protein of a non-typeable strain of Haemophilus Influenzae, which comprises:

transforming a host with a vector as claimed in claim 6, growing the host cell to express the encoded truncated Hia, and isolating and purifying the expressed Hia protein.

- 24. The method of claim 23 wherein the host cell is E. coli.
- 25. The method of claim 23 wherein said encoded truncated Hia is expressed in inclusion bodies.
- 26. The method of claim 25 wherein said isolation and purification of the expressed Hia is effected by:

disrupting the grown transformed cells to produce a supernatant and the inclusion bodies,

solubilizing the inclusion bodies to produce a solution of the recombinant Hia,

chromatographically purifying the solution of recombinant Hia free from cell debris, and

isolating the purified recombinant Hia protein.

27. The method of claim 23 wherein said non-typeable strain of Haemophilus is selected from the group consisting of strains 11, 33, 32, 29, M4071, K9, K22 and 12.

The method of claim 23 wherein said vector includes the T7 promoter and said E. coli is cultured in the presence of an inducing amount of lactose.

29. A pair of nucleotide sequences capable of amplifying and generating a nucleic acid molecule encoding an N-truncated Haemophilus influenzae adhesin (Hia) protein of a strain of Haemophilus influenzae, which pair of nucleotides is selected from the group consisting of:

SEQ ID No: 7 and SEQ ID No: 15 SEQ ID No: 9 and SEQ ID No: 15 SEQ ID No: 11 and SEQ ID No: 15 SEQ ID No: 13 and SEQ ID No: 15 SEQ ID No: 55 and SEQ ID No: 57

; 6-22-01 :10:07AM ;

# (12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

## (19) World Intellectual Property Organization International Bureau



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## (43) International Publication Date 21 September 2000 (21.09.2000)

### **PCT**

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16 March 1999 (16.03.1999)

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16 March 1999 (16.03.1999)

Filed on (71) Applicant (for all designated States except US): CON-NAUGHT LABORATORIES LIMITED [CA/CA]; 1755 Steeles Avenue, Toronto, Ontario M2R 3T4 (CA).

(72) Inventors; and

(75) Inventors/Applicants (for US only): LOOSMORE, Sheena, M. [CA/CA]; 70 Crawford Rose Drive, Aurora, Ontario L4G 4R4 (CA). YANG, Yan-Ping [CA/CA]; Apt. 709, 120 Torresdale Avenue, Willowdale, Ontario M2R 3N7 (CA). KLEIN, Michel, H. [CA/CA]; 16 Munro Boulevard, Willowdale, Ontario M2P 1B9 (CA).

- (74) Agent: STEWART, Michael, I.; Sim & McBurney, 6th Floor, 330 University Avenue, Toronto, Ontario M5G 1R7 (CA).
- (81) Designated States (national): AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, IP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
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#### Published:

with international search report

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: RECOMBINANT HAEMOPHILUS INFLUENZAE ADHESIN PROTEINS

(57) Abstract: Recombinant production of Hia protein, in full-length and N-terminally truncated forms, of non-typeable strains of Haemophilus influenzae, is described. The nucleic acid and deduced amino acid sequences of Hia genes of various strains of non-typeable and type c Haemophilus influenzae also are described.



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	INTERNATIONAL SEARCH	PCT/CA 00/	/00289	4
	DOCUMENTS CONSIDERED TO BE RELEVANT		Relevant to claim No.	┨
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A	the whole document  ST GEME III J W ET AL: "Prevalence and distribution of the hmw and hia genes and the HMW and Hia adhesins among genetically diverse strains of nontypeable Haemophilus influenzae"		1-27	
A	FOR MICROBIOLOGI. WASHINGTON FOR MICROBIOLOGI. WASHINGTON WOOL. 66, no. 1, January 1998 (1998-01), pages 364-368, XP002137980 ISSN: 0019-9567 the whole document  WO 96 02648 A (AMERICAN CYANAMID CO; BACTEX INC (US); GREEN BRUCE A (US); BRINTON) 1 February 1996 (1996-02-01) the whole document		1-27	
A	US 5 843 463 A (KRIVAN HOWARD C ET AL) 1 December 1998 (1998-12-01) the whole document			
3	200 (continuation of second sheet) (July 1992)		a 2 of 2	



International application No. PCT/CA 00/00289

	INTERNATIONAL SEARCH HER STITLE	
	tourned unsearchable (Continuation of item 1 of first sheet)	
ox I	Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)	
his Ir	ernational Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:	
. [	Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:	
≥. [	Claims Nos.:  because they relate to parts of the International Application that do not comply with the prescribed requirements to such because they relate to parts of the International Search can be carried out, specifically:  an extent that no meaningful International Search can be carried out, specifically:	
3.	Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).	
Во	II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)	
Thi	International Searching Authority found multiple inventions in this international application, as follows:	
	see additional sheet	
1.	As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.	
1.	As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.	
	As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.	
3	As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.	

# FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-27 (in part)

An isolated and purified nucleic acid molecule having a sequence as set forth in Seq.Id.No. 23 of the sequence listing, encoding for an aminoacid molecule of an Haemophilus influenzae adhesin having primary structure as set forth in Seq.Id.No.24 of the sequence listing. Vectors for the recombinant production of said adhesin, immunogenic compositions containing the same.

2. Claims: 1-27 (in part)

An isolated and purified nucleic acid molecule having a sequence as set forth in Seq.Id.No. 25 of the sequence listing, encoding for an aminoacid molecule of an Haemophilus influenzae adhesin having primary structure as set forth in Seq.Id.No.26 of the sequence listing. Vectors for the recombinant production of said adhesin, immunogenic compositions containing the same.

3. Claims: 1-27 (in part)

An isolated and purified nucleic acid molecule having a sequence as set forth in Seq.Id.No.27 of the sequence listing, encoding for an aminoacid molecule of an Haemophilus influenzae adhesin having primary structure as set forth in Seq.Id.No.28 of the sequence listing. Vectors for the recombinant production of said adhesin, immunogenic compositions containing the same.

4. Claims: 1-27 (in part)

An isolated and purified nucleic acid molecule having a sequence as set forth in Seq.Id.No.29 of the sequence listing, encoding for an aminoacid molecule of an Haemophilus influenzae adhesin having primary structure as set forth in Seq.Id.No.30 of the sequence listing. Vectors for the recombinant production of said adhesin, immunogenic compositions containing the same.

5. Claims: 1-27 (in part)

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An isolated and purified nucleic acid molecule having a sequence as set forth in Seq.Id.No.31 of the sequence listing, encoding for an aminoacid molecule of an Haemophilus influenzae adhesin having primary structure as set forth in Seq.Id.No.32 of the sequence listing. Vectors for the recombinant production of said adhesin, immunogenic

# FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

compositions containing the same.

6. Claims: 1-27 (in part)

An isolated and purified nucleic acid molecule having a sequence as set forth in Seq.Id.No.33 of the sequence listing, encoding for an aminoacid molecule of an Haemophilus influenzae adhesin having primary structure as set forth in Seq.Id.No.34 of the sequence listing. Vectors for the recombinant production of said adhesin, immunogenic compositions containing the same.

7. Claims: 1-27 (in part)

3

An isolated and purified nucleic acid molecule having a sequence as set forth in Seq.Id.No.35 of the sequence listing, encoding for an aminoacid molecule of an Haemophilus influenzae adhesin having primary structure as set forth in Seq.Id.No.36 of the sequence listing. Vectors for the recombinant production of said adhesin, immunogenic compositions containing the same.

page 2 of 2

Information on patent family members

PCT/CA 00/00289

Patent document		Publication date		ent family ember(s)	Publication date
dted in search report WO 9630519	l	03-10-1996	US AU AU CA EP JP	5646259 A 718392 B 5322896 A 2216292 A 0815236 A 11502713 T	08-07-1997 13-04-2000 16-10-1996 03-10-1996 07-01-1998 09-03-1999
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US 5843463	A	01-12-1998	CA EP JP WO US US AT CA DE DE DK EP ES JP	2138765 A 0647139 A 2805174 B 7509693 T 9400149 A 5721115 A 5679547 A 176989 T 2098598 A 69130955 D 69130955 T 565590 T 0565590 A 2131066 T 6508346 T 9210936 A	06-01-1994 12-04-1995 30-09-1998 26-10-1995 06-01-1994 24-02-1998 21-10-1997 15-03-1999 22-06-1992 08-04-1999 01-07-1999 27-09-1999 20-10-1993 16-07-1999 22-09-1994 09-07-1992

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From the

To:

## PATENT COOPERATION TREATY

**WILL 20 2001** 

8IM & MEBURNEY BIM. HUBHES, ASHTON & MAKAY

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing (day/month/year)

17.07,2001

Applicant's or agent's file reference

international application No.

PCT/CA00/00289

STEWART, Michael I.

330 University Avenue

Toronto, Ontario M5G 1R7

SIM & McBURNEY

1038-1025

6th Floor

CANADA

international filing date (day/month/year)

16/03/2000

Priority date (day/month/year)

IMPORTANT NOTIFICATION

16/03/1999

Applicant

CONNAUGHT LABORATORIES LIMITED et al

INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

- 1. The applicant is hereby notified that this international Preliminary Examining Authority transmits herewith the International preliminary examination report and its annexes, if any, established on the international application.
- 2. A copy of the report and its annexes, if any, is being transmitted to the international Bureau for communication to all the elected Offices.
- 3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

## 4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/

European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d

Fax: +49 69 2399 - 4465

Tel.+49 89 2399-7351

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# PATENT COOPERATION TREATY

# **PCT**

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

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Applicant's or agent's t	ile reference	See Noti	fication of Transmittal of International ary Examination Report (Form PCT/IPEA/418)			
1038-1025						
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Applicant						
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and is transmi	tied to the applicant according to the		International Preliminary Examining Authority			
<ul> <li>This REPORT consists of a total of 9 sheets, including this cover sheet.</li> <li>This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative instructions under the PCT).</li> <li>These annexes consist of a total of 8 sheets.</li> </ul>						
	ontains indications relating to the follow	ving Items:				
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IV 🗵	Lack of unity of invention	isvon of manas diw (c	ty, inventive step or industrial applicability:			
V ⊠	Reasoned statement and explanations suporting su	uch statement	,,	1		
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VIII ☑ Certain observations on the international application						
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Date of submission	on of the damand					
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# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA00/00289

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l.	Basis	of the report	•			have been furnished to			
1.	With regard to the elements of the international application (Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)):  Description, pages:								
	1-13,1 19-63		as originally filed		•				
	14,15	,18	as received on	22/06/2001	with letter of	22/06/2001			
	Claim	ıs, No.:							
	1-29		as received on	22/06/2001	with letter of	22/06/2001			
	Draw	lngs, sheets:							
	1/83-	83/83	as originally filed						
	Sequence listing part of the description, pages:								
	2-75.	filed with the l	etter of 29.05.00						
<ol> <li>With regard to the language, all the elements marked above were available or furnished language in which the international application was filled, unless otherwise indicated united.</li> </ol>									
		These elements were available or furnished to this Authority in the following language: , which is:							
the language of a translation furnished for the purposes of the international search (under Rule 23.  the language of publication of the international application (under Rule 48.3(b)).						rch (under Rule 23.1(b)).			
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	the language of a translation furnished for the purposes of international preliminary examination (under ricis 55.2 and/or 55.3).								
	3. With regard to any nuclectide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:								
		contained in t	he international application	n in written form.		•			
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# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA00/00289

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4.	The	amendments have re	esulted in the cancellation of:	•
		the description,	pages:	
		the cialms.	Nos.:	
		the drawings.	sheets:	
5.	×	This report has been	n established as if (some of) the amendments had not been made, since by ond the disclosure as filed (Rule 70.2(c)):	
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	1.	Statement	•	•

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA00/00289

Novelty (N)

Yes:

Claims 1-2,4-29

No: Claims 3

Inventive step (IS)

Yes: Claims 4

No:

Claims 1-3,5-29

Industrial applicability (IA)

Yes: Claims 1-29

No: Claims

2. Citations and explanations see separate sheet

## VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

# INTERNATIONAL PRELIMINARY

International application No. PCT/CA00/00289

**EXAMINATION REPORT - SEPARATE SHEET** 

D1: WO 96 30519 A (UNIV WASHINGTON ;UNIV ST LOUIS (US); ST GEME JOSEPH W III (US); BA) 3 October 1996 (1996-10-03)

D2: GEME J W S ET AL: 'CHARACTERIZATION OF THE GENETIC LOCUS ENCODING HAEMOPHILUS INFLUENZAE TYPE B SURFACE FIBRILS' JOURNAL OF BACTERIOLOGY, US, WASHINGTON, DC, vol. 178, no. 21, November 1996 (1996-11), pages 6281-6287, XP000863110 ISSN: 0021- 9193

D3: BARENKAMP S J ET AL: 'IDENTIFICATION OF A SECOND FAMILY OF HIGH-MOLECULAR-WEIGHT ADHESION PROTEINS EXPRESSED BY NON-TYPABLE HAEMOPHILUS INFLUENZAE' MOLECULAR MICROBIOLOGY, GB, BLACKWELL SCIENTIFIC, OXFORD, vol. 19, no. 6, 1996, pages 1215-1223, XP000579265 ISSN: 0950-382X

#### Item I

The amendment of Claim 3 is not allowable under Articles 19(2) and 34 (2) (b) PCT. Additional feature "N-truncated protein having the ability to bind to human epithelial cells" is not disclosed in the description as originally filed. For the N-truncated hia proteins it is only described that immunization causes protection against colonization (see Examples).

#### Item IV

The present set of claims are not linked in manner so as to form a single general inventive concept as required under Rule 13(1) PCT.

The problem underlying the invention of the present application is the provision of a set of nucleotide and amino acid sequences of adhesion (Hia) from non-typeable strains of Haemophilus influenzae.

The solution is represented by the set of amino- and nucleic acid sequences as set forth in SEQ. ID. Nos 23-36.

The international patent application WO9630519 discloses adhesins from non-typeable strains of Haemophilus influenzae, as well as methods for their recombinant production



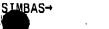
International application No. PCT/CA00/00289 INTERNATIONAL PRELIMINARY **EXAMINATION REPORT - SEPARATE SHEET** 

and their use in immunogenic compositions and production of antibodies (see abstract, example 3, page 82-84).

Genes from non-typeable H. influenzae coding for Hia adhesins are also disclosed by St. Geme et al. in Infection and Immunity (1998, p. 364-368, see abstract).

Therefore the concept of DNA encoding adhesins from non typeable H. influenzae is not new. In consequence, the different adhesins of the present application fall a posteriori into 6 groups of alleged inventions.

- 1. Claims 1-27 (partially)
  - An isolated and purified nucleic acid molecule having a sequence as set forth in SEQ ID NO. 23 encoding an polypeptide of a Haemophlius influenzae adhesion having the primary structure as set forth in SEQ ID NO. 24. Vectors for the recombinant production of said adhesion, immunogenic compositions containing the same.
- An isolated and purified nucleic acid molecule having a sequence as set forth in 2. SEQ ID NO. 27 encoding an polypeptide of a Haemophilus influenzae adhesion having the primary structure as set forth in SEQ ID NO. 28. Vectors for the recombinant production of said adhesion, immunogenic compositions containing the same.
- An isolated and purified nucleic acid molecule having a sequence as set forth in 3. SEQ ID NO. 29 encoding an polypeptide of a Haemophilus influenzae adhesion having the primary structure as set forth in SEQ ID NO. 30. Vectors for the recombinant production of said adhesion, immunogenic compositions containing the same.
- An isolated and purified nucleic acid molecule having a sequence as set forth in 4. SEQ ID NO. 31 encoding an polypeptide of a Haemophilus influenzae adhesion having the primary structure as set forth in SEQ ID NO. 32. Vectors for the recombinant production of said adhesion, immunogenic compositions containing the same.



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# INTERNATIONAL PRELIMINARY International application No. PCT/CA00/00289 EXAMINATION REPORT - SEPARATE SHEET

- 5. An isolated and purified nucleic acid molecule having a sequence as set forth in SEQ ID NO. 33 encoding an polypeptide of a Haemophilus influenzae adhesion having the primary structure as set forth in SEQ ID NO. 34. Vectors for the recombinant production of said adhesion, immunogenic compositions containing the same.
- 6. An isolated and purified nucleic acid molecule having a sequence as set forth in SEQ ID NO. 35 encoding an polypeptide of a Haemophilus influenzae adhesion having the primary structure as set forth in SEQ ID NO. 36. Vectors for the recombinant production of said adhesion, immunogenic compositions containing the same.

### Item V

### 1. Novelty:

Claim 3 is not allowable under Article 33 (2) PCT.

Due to the generic and broad definition (especially the wording "truncated" and "expressible" of said claim (see also item VIII) all sorts of H. influenza adhesion encoding nucleotides fall under the definition of Claim 3.

In other words all adhesion nucleotides encoding for any adhesion being shorter (i.e. truncations of only one or two amino acids) than an adhesion of the present application lies within the definition such as those of D1 (see e.g. sequence comparisons of the Search Examiner page 6, in comparison with GSP:R99394 is shorter than no SEQ ID 28).

## 2. Inventive step

D1 is considered to represent the closest prior art document. D1 teaches
Haemophilus adhesion proteins nucleic acids and derived vaccines. SEQ ID NO,
36 of the present application has 97% identity with the amino acid sequence of
D1, SEQ ID NO 32 has 79% identity with the amino acid sequence of D1
(Sequence Comparisons of the Search Examiner).

The problem of the present application is to provide further H. Influenza adhesions

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International application No. PCT/CA00/00289 INTERNATIONAL PRELIMINARY **EXAMINATION REPORT - SEPARATE SHEET** 

proteins and their encoding genes. As soon as one family member of the Haemophllus influenza adhesion protein, its gene the recombinant production and its immunological use is known, it is routine for a skilled person to determine further similar members from other strains of said proteins their immunogenic fragments and their encoding genes.

In this case the cloning and expression, although requiring much work, does not pose such problems so that there was no reasonable expectation of success. For a skilled person it is also obvious to provide non-specified truncated versions of said genes or proteins having no particular unexpected effect (Claim 3).

In consequence, the present claims 1-3, 5-29 are not allowable under Article 33 (3) PCT.

The specific truncated Hia proteins of Claim 4 fulfil the requirements under Article 33(2) and (3) PCT.

The essential difference with D1 is the truncated form wherein the signal sequence is deleted causing a higher expression in E. coli. Said truncated proteins are still Immunogenic (see Examples).

The problem of the present application can thus be defined as the provision of alternative hia proteins which can be produced recombinantly in a high amount still causing immunity.

The solution i.e. the truncated hia proteins of claim 4 are not derivable from D1 or any other document cited in the Search Report.

### Item VIII

Claim 2 is formulated in terms of a "product by process". In the PCT contracting states no unified criteria exist concerning this type of claims. Before the EPO such 1. claims, defined in terms of a product by process of manufacture are only admissible if the product as such fulfile the requirements of patentability, i.e. If the products are novel and inventive and if the product cannot be defined by true technical features (Article 6 PCT).

The same applies to claim 15.

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SENT BY:SIMBAS

-> Shoemaker & Mattare Ltd.;

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INTERNATIONAL PRELIMINARY **EXAMINATION REPORT - SEPARATE SHEET** 

International application No. PCT/CA00/00289

Independent Claim 3 does not disclose any true technical features. The only 2. characteristic of the claimed nucleic acids is that they are "truncated" and "expressible as inclusion bodies". In consequence, said claim is vague and thus not clear (Article 6 PCT).

The Applicant should prove whether the strains of Claim 27 are known by the 3. skilled person. Otherwise said claim is not clear.



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## PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL SEARCH REPORT

		(PCT Article 18 and Rules 43 and 44	)	•
pplicant's of age	ent's file reference	FOR FURTHER See Notificatio	n of Transmittal of Interna	ational Search Report applicable, hem 5 below.
		ACTION (Form PCI/IS	, , , , , , , , , , , , , , , , , , ,	
038-1025 itemational app	lication No.	International filing date (day/month/year)	(Earliest) Priority D	ate (day/month/year)
			16/	03/1999
CT/ CA 00/	00289	16/03/2000	10/	00/1777
pplicant			•	
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CONNAUGHT	LABORATORIES LI	ATTED		
This internation according to A	nai Search Report has bee rticle 18. A copy is being tr	on prepared by this international Searching anamitted to the international Bureau.	Authority and is transmitt	ed to the applicant
This Internation	nal Search Report consist	of a total of sheets.		
X	it is also accompanied by	y a copy of each prior art document cited in	this report.	
a. With re	second to the lenguage the	e international search was carried out on the nless otherwise indicated under this item.	e basis of the Internations	al application in the
	the international search	was carried out on the basis of a translation		
h With r	poord to enviruelselide s	ind/or amino ecid sequence disclosed in t	the international applicati	on, the international search
was c	arriad out on the Dasis of t	he sequence listing : tional application in written form.		
	COMGINED IN the internet	ternational application in computer readabl	e form.	
H		to this Authority in written form.		
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(X)	international application the statement that the in	n as filed has been furnished. Information recorded in computer readable		
-	fumished			
2.	Certain claims were fo	ound unsearchable (See Box i).		
3. <b>X</b>	Unity of invention is i	acidng (see Box II).		
_			-	
4. With regi	ard to the title,		•	•
X	the text is approved as	submitted by the applicant.		
	the text has been estal	dished by this Authority to read as follows:		• .
5. With reg	ard to the abstract,			
X	the text is approved as	submitted by the applicant. blished, according to Rule 38.2(b), by this the date of mailing of this international set	Authority as it appears in arch report, submit comm	Box III. The applicant may, sents to this Authority.
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6. The figu		sublished with the abstract is Figure No.	Ĺ	None of the figures.
ᅵ	as suggested by the a		_	
		falled to suggest a figure.		
	pecanse sus signes be	nter characterizes the invention.		

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## INTERNATIONAL SEARCH REPORT

International Application No PCT/CA 00/00289

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 CO7K14/285 C12N15/00 A61K38/00

According to international Patent Classification (IPC) or to both national classification and IPC

#### B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols) IPC 7 CO7K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

STRAND, WPI Data, EPO-Internal, BIOSIS

C. DOCUME	Relevant to claim No.	
Category *	WO 96 30519 A (UNIV WASHINGTON; UNIV ST	1-27
^	LOUIS (US); ST GEME JOSEPH W III (US); BA) 3 October 1996 (1996-10-03) abstract example 3 page 82 -page 84	
X	GEME J W S ET AL: "CHARACTERIZATION OF THE GENETIC LOCUS ENCODING HAEMOPHILUS INFLUENZAE TYPE B SURFACE FIBRILS" JOURNAL OF BACTERIOLOGY, US, WASHINGTON, DC, vol. 178, no. 21, November 1996 (1996-11), pages 6281-6287, XP000863110 ISSN: 0021-9193 the whole document	1-27
	-/	

Further documents are listed in the continuation of box C.	Patent tamily members are listed in annex.
*A* document defining the general state of the art which is not  *A* document defining the general state of the art which is not  *E* earlier document but published on or after the intermational filing date  *L* document which may throw doubts on priority claim(s) or "thing is a state of earlier and the state of the publication date of another other means  *O* document referring to an oral disclosure, task, commission or other means  *A* document referring to an oral disclosure, task, commission or other means  *A* document referring to an oral disclosure, task, commission or other means  *A* document referring to an oral disclosure, task, commission or other means.	The later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the limention.  "X" comment of particular responses; the claimed invention involve an inventive step when the document is taken alone involve an inventive step when the claimed invention document of particular response; the claimed invention ments, such combination being covious to a person ordered in the star.  "5" document Westerd of the same parent tensity tensity.  "5" document westerd of the international search report
Date of the actual completion of the international search  13 February 2001	2 0. 2. 01
Name and making address of the ISA  European Petent Office, P.B. 5818 Patentiaen 2  NL - 2280 HV Rijawijk  Tel. (+81-70) 340-2040, Tx. 31 651 epo ni, Fax: (+31-70) 840-9016	Panzica, G

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## INTERNATIONAL SEARCH REPORT

International Application No PCT/CA 00/00289

	PCT/CA 00/00289			
	tion) DOCUMENTS CONSIDERED TO BE RELEVANT	<u> </u>		
atenory *	Citation of document, with indication, where appropriate, of the relevant passages		Relevant to claim No.	
	BARENKAMP S J ET AL: "IDENTIFICATION OF A SECOND FAMILY OF HIGH-MOLECULAR-WEIGHT ADHESION PROTEINS EXPRESSED BY NON-TYPABLE		1-27	
	HAEMOPHILUS INFLUENZAE" MOLECULAR MICROBIOLOGY,GB,BLACKWELL SCIENTIFIC, OXFORD, vol. 19, no. 6, 1996, pages 1215-1223, XP000579265 ISSN: 0950-382X the whole document		`	
A	ST GEME III J W ET AL: "Prevalence and distribution of the hmw and his genes and the HMW and His adhesins among genetically diverse strains of nontypeable Haemophilus influence" INFECTION AND IMMUNITY US AMERICAN SOCIETY		1-27	
	FOR MICROBIOLOGY. WASHINGTON, vol. 66, no. 1, January 1998 (1998-01), pages 364-368, XP002137980 the whole document		1-27	
A	WO 96 02648 A (AMERICAN CYANAMID CO; BACTEX INC (US); GREEN BRUCE A (US); BRINTON) 1 February 1996 (1996-02-01) the whole document		1-27	
A	US 5 843 463 A (KRIVAN HOWARD C ET AL) 1 December 1998 (1998-12-01) the whole document		1-61	
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Form PCT/ABA/210 (continuation of second sheet) (July 1992)

7034150813;#19

International Application No. PCT/CA 00 00289

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-27 (in part)

An isolated and purified nucleic acid molecule having a sequence as set forth in Seq.Id.No. 23 of the sequence listing, encoding for an aminoacid molecule of an Haemophilus influenzae adhesin having primary structure as set forth in Seq.Id.No.24 of the sequence listing. Vectors for the recombinant production of said adhesin, immunogenic compositions containing the same.

2. Claims: 1-27 (in part)

An isolated and purified nucleic acid molecule having a sequence as set forth in Seq.Id.No. 25 of the sequence listing, encoding for an aminoacid molecule of an Haemophilus influenzae adhesin having primary structure as set forth in Seq.Id.No.26 of the sequence listing. Vectors for the recombinant production of said adhesin, immunogenic compositions containing the same.

3. Claims: 1-27 (in part)

An isolated and purified nucleic acid molecule having a sequence as set forth in Seq.Id.No.27 of the sequence listing, encoding for an aminoacid molecule of an Haemophilus influenzae adhesin having primary structure as set forth in Seq.Id.No.28 of the sequence listing. Vectors for the recombinant production of said adhesin, immunogenic compositions containing the same.

4. Claims: 1-27 (in part)

An isolated and purified nucleic acid molecule having a sequence as set forth in Seq.Id.No.29 of the sequence listing, encoding for an aminoacid molecule of an Haemophilus influenzae adhesin having primary structure as set forth in Seq.Id.No.30 of the sequence listing. Vectors for the recombinant production of said adhesin, immunogenic compositions containing the same.

5. Claims: 1-27 (in part)

An isolated and purified nucleic acid molecule having a sequence as set forth in Seq.Id.No.31 of the sequence listing, encoding for an aminoacid molecule of an Haemophilus influenzae adhesin having primary structure as set forth in Seq.Id.No.32 of the sequence listing. Vectors for the recombinant production of said adhesin, immunogenic

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International Application No. PCT.CA 00 00289

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

compositions containing the same.

### 6. Claims: 1-27 (in part)

An isolated and purified nucleic acid molecule having a sequence as set forth in Seq.Id.No.33 of the sequence listing, encoding for an aminoacid molecule of an Haemophilus influenzae adhesin having primary structure as set forth in Seq.Id.No.34 of the sequence listing. Vectors for the recombinant production of said adhesin, immunogenic compositions containing the same.

### 7. Claims: 1-27 (in part)

An isolated and purified nucleic acid molecule having a sequence as set forth in Seq.Id.No.35 of the sequence listing, encoding for an aminoacid molecule of an Haemophilus influenzae adhesin having primary structure as set forth in Seq.Id.No.36 of the sequence listing. Vectors for the recombinant production of said adhesin, immunogenic compositions containing the same.

page 2 of 2

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# INTERNATIONAL SEARCH REPORT

International application No. PCT/CA 00/00289

INTERNATIONAL SEATISTICS	
Box I Observations where certain claims were found unsearchable (Continu	ustion of item 1 of first aheet)
This international Search Report has not been established in respect of certain daims under	1
Claims Nos.:     because they relate to subject matter not required to be searched by this Authority,	namely:
Claims Nos.:     because they relate to parts of the international Application that do not comply with an extent that no meaningful international Search can be carried out, specifically:	n the prescribed requirements to such
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the se	
Box II Observations where unity of invention is lacking (Continuation of t	tem 2 of first sheet)
This international Searching Authority found multiple inventions in this international applic	
see additional sheet	
As all required additional search fees were timely paid by the applicant, this introduced searchable dalms.	ernational Search Report covers ali
2. As all searchable dialins could be searched without effort justifying an addition of any additional fee.	al tee, this Authority did not invite payment
3. As only some of the required additional search fees were timely paid by the a covers only those claims for which fees were paid, specifically claims Nos.:	pplicant, this international Search Report
No required additional search fees were timely paid by the applicant. Consequently paid by the applicant consequence of the covered by claim restricted to the invention first mentioned in the claims; it is covered by claim.	quently, this international Search Report is is Nos.:
Remark on Process	eas were accompanied by the applicant's protest.  ed the psyment of additional search fees.

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SENT BY:SIMBAS

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## INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No PCT/CA 00/00289

Patent document cited in search report	Publication date	Patent family member(e)	Publication date
WO 9630519 A	03-10-1996	US 5646259 A AU 718392 B AU 5322896 A CA 2216292 A EP 0815236 A JP 11502713 T	08-07-1997 13-04-2000 16-10-1996 03-10-1996 07-01-1998 09-03-1999
WO 9602648 A	01-02-1996	US 5643725 A US 5834187 A US 5968769 A AU 706937 B AU 3097295 A CA 2195090 A EP 0771352 A	01-07-1997 10-11-1998 19-10-1999 01-07-1999 16-02-1996 01-02-1996 07-05-1997
US 5843463 A	01-12-1998	CA 2138765 A EP 0647139 A JP 2805174 B JP 7509693 T WO 9400149 A US 5721115 A US 5679547 A AT 176989 T CA 2098598 A DE 69130955 D DE 69130955 T DK 565590 T EP 0565590 A ES 2131066 T JP 6508346 T WO 9210936 A	06-01-1994 12-04-1995 30-09-1998 26-10-1995 06-01-1994 24-02-1998 21-10-1997 15-03-1999 22-06-1992 08-04-1999 01-07-1999 27-09-1999 22-09-1999

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## PATENT COOPERATION TREATY

RECEIVED

PC BIM & MCBURNEY

FEB 26 2001

From the INTERNATIONAL SEARCHING AUTHORITY

To: SIM & McBURNEY Attn. Stewart, Michael, I. 330 University Avenue

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

6th Floor Toronto, Ontario M5G 1R7 CANADA	(PCT Rule 44.1)		
	Date of mailing (day/month/year) 20/02/2001		
1038-1025	FOR FURINER ACTION		
International application No. PCT/CA 00/ 00289	international filing date (day/month/year) 16/03/2000		
Applicant			
CONNAUGHT LABORATORIES LIMITED			

1.	$\square$	The appl	icant is hereby n	otified that the international Searon Report has been established and is the commission
	_	Filing of The appl	amendments a icant is entitled, i	nd statement under Article 19: f he so wishes, to amend the cisims of the International Application (see Rule 48):
		When?	The time limit for international Se	or filing such amendments is normally 2 months from the date of transmittal of the sarch Report; however, for more details, see the notes on the accompanying sheet.
		Where?	Directly to the	International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Fascimile No.: (41-22) 740.14/35
		For mos	e detailed instr	uctions, see the notes on the accompanying sheet.
2	· 🗆	The app Article 1	dicant is hereby r 7(2)(a) to that eff	notified that no International Search Report will be cetablished and केले क्षेट केडोबलडेडर अस्टिट- lect is transmitted herewith.
3		With re	gard to the prot	est against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:
			_	r with the decision thereon has been transmitted to the international Bureau together with the to forward the texts of both the protest and the decision thereon to the designated Offices.
		no	decision has be	en made yet on the protest; the applicant will be notified as soon as a decision is made.
١.	4. Fui	rther actio		olicant is reminded of the following:
	H P	the applic righty clai empletion	eant wishes to av m, must reach th of the technical	the priority date, the international application will be published by the international Bureau. old or postpone publication, a notice of withdrawal of the international application, or of the elementarional Bureau as provided in Rules 80 <i>bis.</i> 1 and 90 <i>bis.</i> 3, respectively, before the preparations for international publication.
	Wi	thin 19 mo	onthé from the p postpone the enti	nority date, a demand fer international preliminary examination must be filed if the applicant by into the national phase until 30 months from the priority date (in some Offices even later).
	W	thin 20 m	onthe from the p	riority date, the applicant must perform the prescribed acts for entry into the national phase is which have not been elected in the demand or in a later election within 19 months from the elected because they are not bound by Chapter II.

Name and mailing address of the international Searching Authority

European Patent Office, P.B. 5816 Patentiaan 2 NL-2280 HV Rijawijk Tel. (+31-70) 340-2040, Tx. 31 651 epo ni, Fax: (+31-70) 340-3016

**Authorized officer** 

Chantal Meyer

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#### NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic Instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative instructions, respectively.

#### INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

#### What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the International phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

#### When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the international Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 48.1).

#### Where not to file the emendments?

The amendments may only be filed with the international Bureau and not with the receiving Office or the international Searching Authority (Rule 48.2).

Where a demand for international preliminary examination has been/is filed, see below.

#### How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabio numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

#### What documents must/may accompany the amendments?

#### Latter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

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#### NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended, it must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (III) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

# The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

- [Where originally there were 48 claims and after amendment of some claims there are 51]:
   "Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 38 unchanged; new claims 49 to 51 added."
- (Where originally there were 15 claims and after amendment of all claims there are 11): "Claims 1 to 15 replaced by amended claims 1 to 11."
- 3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
  "Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
  "Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
- 4. [Where various kinds of amendments are made]: "Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 18 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

#### "Statement under article 18(1)" (Rule 48.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 600 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

#### Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preterably, at the time of filing the amendments (and any statement) with the international Bureau, also file with the international Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

### Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.



(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference  1038-1025	FOR FURTHER see Notification of (Form PCT/ISA/2	of Transmittal of International Search Report 220) as well as, where applicable, item 5 below.
International application No.	International filing date (day/month/year)	(Earliest) Priority Date (day/month/year)
PCT/CA 00/00289	16/03/2000	16/03/1999
Applicant		
CONNAUGHT LABORATORIES LI	MITED	
This International Search Report has bee according to Article 18. A copy is being tr	en prepared by this International Searching Auth ansmitted to the International Bureau.	nority and is transmitted to the applicant
This International Search Report consists  [X] It is also accompanied by	of a total of sheets.  va copy of each prior art document cited in this	report.
Basis of the report		
	international search was carried out on the bas less otherwise indicated under this item.	sis of the international application in the
the international search v Authority (Rule 23.1(b)).	vas carried out on the basis of a translation of th	he international application furnished to this
was carried out on the basis of th	e sequence listing :	ternational application, the international search
[	onal application in written form. ernational application in computer readable forn	n
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X the statement that the su	bsequently furnished written sequence listing das filed has been furnished.	oes not go beyond the disclosure in the
the statement that the inf furnished	ormation recorded in computer readable form is	s identical to the written sequence listing has been
	and unsearchable (See Box I).	
3. X Unity of invention is lac	king (see Box II).	
4. With regard to the title,		
$oxed{X}$ the text is approved as su	ubmitted by the applicant.	
the text has been establis	shed by this Authority to read as follows:	
5. With regard to the abstract,		
	ubmitted by the applicant. shed, according to Rule 38.2(b), by this Authorit	by as it appears in Boy III. The applicant may
	e date of mailing of this international search rep	
6. The figure of the <b>drawings</b> to be pub	<b>u</b>	
as suggested by the appl		X None of the figures.
because the applicant fai	•	
because this figure better	r characterizes the invention.	

Form PCT/ISA/210 (first sheet) (July 1998)

International Application No. PCT/CA 00/00289

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C07K14/285 C12N15/00 A61K38/00

According to International Patent Classification (IPC) or to both national classification and IPC

#### B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  $IPC \ 7 \ C07K$ 

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

STRAND, WPI Data, EPO-Internal, BIOSIS

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 30519 A (UNIV WASHINGTON ;UNIV ST LOUIS (US); ST GEME JOSEPH W III (US); BA) 3 October 1996 (1996-10-03) abstract example 3 page 82 -page 84	1-27
X	GEME J W S ET AL: "CHARACTERIZATION OF THE GENETIC LOCUS ENCODING HAEMOPHILUS INFLUENZAE TYPE B SURFACE FIBRILS" JOURNAL OF BACTERIOLOGY, US, WASHINGTON, DC, vol. 178, no. 21, November 1996 (1996-11), pages 6281-6287, XP000863110 ISSN: 0021-9193 the whole document	1-27

X Further documents are listed in the continuation of box C.	Patent family members are listed in annex.
<ul> <li>Special categories of cited documents:</li> <li>"A" document defining the general state of the art which is not considered to be of particular relevance</li> <li>"E" earlier document but published on or after the international filing date</li> <li>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</li> <li>"O" document referring to an oral disclosure, use, exhibition or other means</li> <li>"P" document published prior to the international filing date but later than the priority date claimed</li> </ul>	<ul> <li>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</li> <li>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</li> <li>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</li> <li>"&amp;" document member of the same patent family</li> </ul>
Date of the actual completion of the international search  13 February 2001	Date of mailing of the international search report  2 0. 2. 0 1
Name and mailing address of the ISA  European Patent Office, P.B. 5818 Patentlaan 2  NL - 2280 HV Rijswijk  Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  Fax: (+31-70) 340-3016	Authorized officer Panzica, G

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International Application No PCT/CA 00/00289

Category °	ation) DOCUMENTS CONSIDERED TO BE RELEVANT  Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
acegory "	oration of document, with indication, where appropriate, of the relevant passages	Helevant to claim No.
(	BARENKAMP S J ET AL: "IDENTIFICATION OF A SECOND FAMILY OF HIGH-MOLECULAR-WEIGHT ADHESION PROTEINS EXPRESSED BY NON-TYPABLE HAEMOPHILUS INFLUENZAE" MOLECULAR MICROBIOLOGY, GB, BLACKWELL SCIENTIFIC, OXFORD, vol. 19, no. 6, 1996, pages 1215-1223, XP000579265 ISSN: 0950-382X the whole document	1-27
	ST GEME III J W ET AL: "Prevalence and distribution of the hmw and hia genes and the HMW and Hia adhesins among genetically diverse strains of nontypeable Haemophilus influenzae"  INFECTION AND IMMUNITY, US, AMERICAN SOCIETY FOR MICROBIOLOGY. WASHINGTON, vol. 66, no. 1, January 1998 (1998-01), pages 364-368, XP002137980  ISSN: 0019-9567 the whole document	1-27
A	WO 96 02648 A (AMERICAN CYANAMID CO;BACTEX INC (US); GREEN BRUCE A (US); BRINTON) 1 February 1996 (1996-02-01) the whole document	1-27
A	US 5 843 463 A (KRIVAN HOWARD C ET AL) 1 December 1998 (1998-12-01) the whole document	1-27

#### FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-27 (in part)

An isolated and purified nucleic acid molecule having a sequence as set forth in Seq.Id.No. 23 of the sequence listing, encoding for an aminoacid molecule of an Haemophilus influenzae adhesin having primary structure as set forth in Seq.Id.No.24 of the sequence listing. Vectors for the recombinant production of said adhesin, immunogenic compositions containing the same.

2. Claims: 1-27 (in part)

An isolated and purified nucleic acid molecule having a sequence as set forth in Seq.Id.No. 25 of the sequence listing, encoding for an aminoacid molecule of an Haemophilus influenzae adhesin having primary structure as set forth in Seq.Id.No.26 of the sequence listing. Vectors for the recombinant production of said adhesin, immunogenic compositions containing the same.

3. Claims: 1-27 (in part)

An isolated and purified nucleic acid molecule having a sequence as set forth in Seq.Id.No.27 of the sequence listing, encoding for an aminoacid molecule of an Haemophilus influenzae adhesin having primary structure as set forth in Seq.Id.No.28 of the sequence listing. Vectors for the recombinant production of said adhesin, immunogenic compositions containing the same.

4. Claims: 1-27 (in part)

An isolated and purified nucleic acid molecule having a sequence as set forth in Seq.Id.No.29 of the sequence listing, encoding for an aminoacid molecule of an Haemophilus influenzae adhesin having primary structure as set forth in Seq.Id.No.30 of the sequence listing. Vectors for the recombinant production of said adhesin, immunogenic compositions containing the same.

5. Claims: 1-27 (in part)

An isolated and purified nucleic acid molecule having a sequence as set forth in Seq.Id.No.31 of the sequence listing, encoding for an aminoacid molecule of an Haemophilus influenzae adhesin having primary structure as set forth in Seq.Id.No.32 of the sequence listing. Vectors for the recombinant production of said adhesin, immunogenic

#### FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

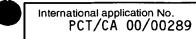
compositions containing the same.

#### 6. Claims: 1-27 (in part)

An isolated and purified nucleic acid molecule having a sequence as set forth in Seq.Id.No.33 of the sequence listing, encoding for an aminoacid molecule of an Haemophilus influenzae adhesin having primary structure as set forth in Seq.Id.No.34 of the sequence listing. Vectors for the recombinant production of said adhesin, immunogenic compositions containing the same.

#### 7. Claims: 1-27 (in part)

An isolated and purified nucleic acid molecule having a sequence as set forth in Seq.Id.No.35 of the sequence listing, encoding for an aminoacid molecule of an Haemophilus influenzae adhesin having primary structure as set forth in Seq.Id.No.36 of the sequence listing. Vectors for the recombinant production of said adhesin, immunogenic compositions containing the same.



Box I Observations where certain claims were found unsearchable (Conti	nuation of item 1 of first sheet)
This International Search Report has not been established in respect of certain claims under	er Article 17(2)(a) for the following reasons:
Claims Nos.:     because they relate to subject matter not required to be searched by this Authority	y, namely:
Claims Nos.:     because they relate to parts of the International Application that do not comply with an extent that no meaningful International Search can be carried out, specifically:	h the prescribed requirements to such
Claims Nos.:     because they are dependent claims and are not drafted in accordance with the se	
Box II Observations where unity of invention is lacking (Continuation of it	em 2 of first sheet)
This International Searching Authority found multiple inventions in this international applica	tion, as follows:
see additional sheet	
As all required additional search fees were timely paid by the applicant, this International searchable claims.	ational Search Report covers all
2. As all searchable claims could be searched without effort justifying an additional for of any additional fee.	ee, this Authority did not invite payment
3. As only some of the required additional search fees were timely paid by the applic covers only those claims for which fees were paid, specifically claims Nos.:	ant, this International Search Report
4. No required additional search fees were timely paid by the applicant. Consequent restricted to the invention first mentioned in the claims; it is covered by claims Nos	ly, this International Search Report is 3.:
	ere accompanied by the applicant's protest.  payment of additional search fees.

formation on patent family members

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